



4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2014-N-0199]

MK Laboratories, Inc., et al.; Proposal to Withdraw Approval of Three Abbreviated New Drug Applications for Propoxyphene Products; Opportunity for a Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) is proposing to withdraw approval of three abbreviated new drug applications (ANDAs) for propoxyphene drug products from multiple sources and is announcing an opportunity for holders of those ANDAs to request a hearing on this proposal.

DATES: Submit written requests for a hearing by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]; submit data and information in support of the hearing request by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: Requests for a hearing, supporting data, and other comments are to be identified with Docket No. FDA-2014-N-0199 and submitted to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: David Joy, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6254, Silver Spring, MD 20993-0002, 301-796-3601.

SUPPLEMENTARY INFORMATION:

Propoxyphene is an opioid pain relief medication first approved by FDA in 1957. It has been marketed as a single active ingredient drug product and in combination with other active ingredients such as acetaminophen. It has been marketed under brand names such as Darvon and Darvocet and in generic forms.

After receiving clinical data and other information showing that propoxyphene puts patients at risk of potentially serious and even fatal heart rhythm abnormalities, FDA determined that the risks of propoxyphene outweigh its benefits. On November 18, 2010, FDA asked Xanodyne Pharmaceuticals, Inc. (Xanodyne), the maker of Darvon and Darvocet, and manufacturers of then marketed generic propoxyphene drug products to voluntarily withdraw their products from the U.S. market. In a separate notice published elsewhere in this issue of the Federal Register, FDA is withdrawing approval of 8 NDAs and 46 ANDAs from multiple sources, whose application holders have agreed in writing to permit FDA to withdraw approval of the applications and have waived their opportunity for a hearing.

Although the holders of the approved applications listed in Table 1 are believed to have discontinued marketing these products prior to November 2010, FDA has not received correspondence from these application holders requesting that the Agency withdraw approval of the identified applications. Hence, in accordance with section 505(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(e)), we hereby notify the application holders listed in Table 1 of their opportunity to request a hearing on CDER's proposal to withdraw approval of the listed applications.

Table 1:--Propoxyphene Drug Product Applications for Which FDA Proposes to Withdraw Approval

Application No.	Drug	Applicant or Holder
ANDA 083544	Kesso-Gesic (propoxyphene hydrochloride (HCl)) Capsules, 65 milligrams (mg)	MK Laboratories Inc., 424 Grasmere Ave., Fairfield, CT 06430
ANDA 084551	Propoxyphene HCl Capsules, 65 mg	Whitworth Towne Paulsen Inc.
ANDA 084553	Compound 65 (aspirin, caffeine, and propoxyphene HCl) Capsules, 389 mg/32.4 mg/65 mg	Alra Labs, 3850 Clearview Ct., Gurnee, IL 60031

I. Safety Concern

NDA 010996 and 010997 for propoxyphene HCl alone and in combination with aspirin and caffeine, both held by Xanodyne, were initially approved in 1957 solely on the basis of safety. The 1962 amendments to the FD&C Act required that drugs be shown to be effective as well as safe. To implement the 1962 amendments, FDA initiated the Drug Efficacy Study Implementation (DESI) review to evaluate the effectiveness of drugs that had been previously approved on safety grounds alone. In its DESI review of propoxyphene HCl; propoxyphene HCl with aspirin; and propoxyphene HCl with aspirin, phenacetin, and caffeine, FDA concluded that these drugs were effective for the relief of mild to moderate pain (34 FR 6264, April 8, 1969).

In January 2009, FDA held a joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to address the safety and efficacy of propoxyphene and propoxyphene combination products for the treatment of mild to moderate pain. The committee members voted 14 to 12 against the continued marketing of propoxyphene products but noted that additional information about the drug's cardiac effects would be relevant in weighing its risks and benefits. Using authority under the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110-85), FDA required Xanodyne to conduct a safety study of the effects of propoxyphene on the heart at higher than recommended doses.

Before proceeding with the cardiac safety study, the company first conducted a study on healthy volunteers to determine an appropriate dose. In this study, the healthy volunteers in one group were given a total daily dose of 600 mg of propoxyphene (the maximum approved dose), and volunteers in the second group were given a total daily dose of 900 mg (a dose higher than recommended in product labeling). The results showed that there were significant changes to the electrical activity of the heart (prolonged PR interval, widened QRS complex, and prolonged QT interval), at both the 600 and 900 mg doses. These changes, which can be seen on an electrocardiogram, can increase the risk for serious abnormal heart rhythms. In light of these new scientific findings, CDER determined the postmarketing safety signals for this drug have taken on new importance, and the overall balance of risk and benefit can no longer be considered favorable. Memoranda explaining CDER's determination are available on FDA's Web site and will be placed in Docket No. FDA-2014-N-0199 (Refs. 1 and 2).

On November 19, 2010, FDA issued a Drug Safety Communication recommending against the continued prescription and use of propoxyphene drug products. This recommendation was based on all available data, including the new data showing that when propoxyphene is taken at therapeutic doses, it can cause significant changes to the electrical activity of the heart. FDA has concluded that this safety risk outweighs propoxyphene's benefits for pain relief at recommended doses. Based on this information, FDA asked the manufacturers of currently marketed propoxyphene products to voluntarily remove their products from the market.

Therefore, based on all available data, notice is given to the holders of the approved applications listed in Table 1 and to all other interested persons that the Director of CDER proposes to issue an order, under section 505(e) of the FD&C Act, withdrawing approval of the

applications, amendments, and supplements upon the grounds that scientific data show the listed drugs are unsafe under the conditions of use for which they were approved.

II. Hearing Procedures

In accordance with section 505(e) of the FD&C Act, the applicants are hereby provided an opportunity to request a hearing to show why approval of the applications listed in Table 1 should not be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of the drug products covered by these applications.

An applicant who decides to seek a hearing must file the following: (1) a written notice of participation and request for hearing (see DATES) and (2) the data, information, and analyses relied on to demonstrate that there is a genuine and substantial issue of fact that requires a hearing to resolve (see DATES). Any other interested person may also submit comments on this notice. The procedures and requirements governing this notice of opportunity for a hearing, notice of participation and request for a hearing, the information and analyses to justify a hearing, other comments, and a grant or denial of a hearing are contained in § 314.200 (21 CFR 314.200) and in 21 CFR part 12.

The failure of an applicant to file a timely written notice of participation and request for a hearing, as required by § 314.200, constitutes an election by that applicant not to avail itself of the opportunity for a hearing concerning CDER's proposal to withdraw approval of the applications and constitutes a waiver of any contentions concerning the legal status of the drug products. FDA will then withdraw approval of the applications, and the drug products may not thereafter be lawfully introduced or delivered for introduction into interstate commerce. Any new drug product introduced or delivered for introduction into interstate commerce without an approved application is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If a request for a hearing is not complete or is not supported, the Commissioner of Food and Drugs will enter summary judgment against the person who requests the hearing, making findings and conclusions, and denying a hearing.

All submissions under this notice of opportunity for a hearing must be filed in four copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen in the Division of Dockets Management (see ADDRESSES) between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

This notice is issued under section 505(e) of the FD&C Act and under the authority delegated to the Director of CDER by the Commissioner of Food and Drugs.

III. References

FDA has placed the following references on display in the Division of Dockets Management (see ADDRESSES). They may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at <http://www.regulations.gov>.

1. Memorandum to Dr. Woodcock: Recommendation on a Regulatory Decision for Propoxyphene-Containing Products (November 18, 2010, Hertz and Avigan); <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM234349.pdf>.

2. Memorandum to Dr. Woodcock on Propoxyphene-Containing Products (November 18, 2010, Rappaport);

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM234340.pdf>.

Dated: March 4, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

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